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State-of-the-Art Paper

Selecting Patients for Cardiac Resynchronization Therapy

The Fallacy of Echocardiographic Dyssynchrony

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Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with heart failure. International guidelines unanimously endorse QRS prolongation to identify candidates for implantation, based on over 4,000 patients randomized in landmark trials. Small, observational, nonrandomized studies with surrogate end points have promoted echocardiography as a superior method of patient selection. Over 30 dyssynchrony parameters have been proposed. Most lack validation in appropriate clinical settings, including demonstration of short- and long-term reproducibility and intra- and interobserver variability. Prospective multicenter trials have proved informative in unexpected ways. In core laboratories, parameters exhibit striking variability, poor reproducibility, and limited predictive power. We are concerned that many centers today are using these techniques to select patients for CRT. Publication density and bias have misinformed clinical decision making. Echocardiographic parameters have no place in denying potentially life-saving treatment or in exposing patients to unnecessary risks and draining health care resources. Such measures should not stray beyond the research environment unless validated in randomized trials with robust clinical end points. The electrocardiogram remains a simple, inexpensive, and reproducible tool that identifies patients likely to benefit from CRT. Patient selection must use the parameter prospectively validated in landmark clinical trials: the QRS duration. (J Am Coll Cardiol 2009;53:1944–59) © 2009 by the American College of Cardiology Foundation

Clinical trials of cardiac resynchronization therapy (CRT) have demonstrated unequivocal improvements in functional status, morbidity, and mortality (Table 1) (1–10). International guidelines from both Europe and North America are unanimous in assigning the highest grade of recommendation (11–15). All guidelines state clearly and simply who should receive CRT. Reflecting the landmark clinical trials, patients should have impaired functional status (New York Heart Association [NYHA] functional class III or IV), reduced left ventricular ejection fraction (LVEF) (≤0.35), and prolonged QRS duration (≥120 ms).

Despite these considered recommendations, many clinicians have rejected international guidelines in favor of echocardiographic selection criteria. "Reasons" include the observation that one-third of patients fail to improve clinically or exhibit favorable echocardiographic remodeling (so-called "nonresponders"). It has been suggested that echocardiographic measures of mechanical dyssynchrony may better identify those likely to respond (16,17). Multiple echocardiographic techniques have been proposed with a plethora of publications extolling the virtues of each.

We review the current status of selecting candidates for CRT. What constitutes "response?" What are the strengths and weaknesses of echocardiographic indexes of dyssynchrony? How robust are techniques beyond the research environment? Should patients fulfilling accepted criteria but without echocardiographic dyssynchrony be denied life-saving treatment? Should patients with narrow QRS complexes and echocardiographic dyssynchrony undergo invasive and costly procedures?

The Problem With "Response"

One-quarter to -half of patients are labeled clinical or volumetric "nonresponders." The latter are more frequent, largely due to selected volumetric cutoffs and varying definitions of clinical response. However, failing to achieve specific "response" criteria is not necessarily "nonresponse." Without CRT a patient may have undergone further adverse remodeling, had more limited exercise tolerance, or even be dead. A crucial weakness of echocardiographic studies is the absence of hard clinical end points—all-cause mortality, cardiovascular death, and hospitalizations.

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"Response" is itself a flawed dichotomy. All medical therapies present a continuous spectrum ranging from harm to benefit. Clinical practice is guided by evidence, the highest level of which derives from randomized controlled trials. The end points of these trials reflect the net effect in a population fulfilling specific inclusion criteria. At the patient level, individuals either improve, are unchanged, or deteriorate. No intervention benefits all patients. In populations with heart failure (HF), angiotensin-converting enzyme inhibitors cause reverse remodeling, improve symptoms, and reduce mortality. However, not every individual demonstrates reverse remodeling and improved symptoms. Some individuals may experience hypotension, renal impairment, or hyperkalemia. On the basis of the evidence in populations, we prescribe angiotensin-converting enzyme inhibitors for patients with HF. We do not dwell on selecting which patients will benefit. The arguments apply equally to drugs and devices. Both should be provided to patients fulfilling the inclusion criteria of landmark clinical trials. Differences in health economics threaten these principles. Unlike drugs, the majority of the lifetime cost for devices is incurred at implantation. Identifying so-called "nonresponders" is, therefore, attractive to governments, health services, and other payers.

Clinical Response

Clinical response is variably defined, often without hard clinical end points such as hospitalization or mortality. The original clinical composite score combined measures of functional status with major adverse clinical outcomes (death, hospitalization) and withdrawal of study medication relating to worsening HF (18). However, a plethora of different clinical composite end points have emerged, with components including 6-min walking distance (19–27), peak oxygen consumption (20,28), quality-of-life scores (22,29), and transplantation (19,23,30). Moreover, clinical measures are subject to placebo effect: 39% of control subjects as well as 67% of the treatment group were responders in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study (5).

Volumetric Response

Surrogate end points are just that—surrogates. Volumetric measures reduce sample size, provide mechanistic insights, and are objective. The direction and magnitude of remodeling relates proportionally to survival (31). Changes in left ventricular (LV) volumes may coincide with clinical improvement after implantation (21,30,32). However, definitions of both remodeling and clinical response are varied, and magnitude of either may not reach a specific threshold. Clinical response may occur without volumetric change, or vice versa. Correlations between the 2 are limited. In the MIRACLE trial, change in LV end-diastolic volume and NYHA functional class correlated weakly ($r = 0.13$, $p = 0.02$) (33). Reverse remodeling is greater in patients with nonischemic cardiomyopathy (33,34), whereas clinical outcomes improve irrespective of HF etiology (5,9,10). Furthermore, echocardiographic indexes predict clinical response less accurately than reverse remodeling (21,22). These disparities all caution against substituting remodeling for clinical efficacy. Yu et al. (35) justified the use of echocardiographic outcomes by reporting that reverse remodeling, but not "soft" clinical parameters, predicted 1-year mortality in 141 patients. However, after multivariable adjustment, baseline dyssynchrony assessed using tissue Doppler also failed to predict survival.

Reasons for "Nonresponse"

The benefits of CRT are not solely attributable to correction of baseline dyssynchrony. Numerous factors determine response, each varying between individuals: pacing site, ischemia and scar burden, irreparable dysfunction, device optimization, and subsequent medical progress. How much each variable contributes to nonresponse is unknown. Only a small proportion of the variance in response may relate to baseline dyssynchrony.

Lateral lead placement improves reverse remodeling and functional capacity compared with anterior locations (36–38). Tailoring lead position to the area of maximal mechanical delay has also been advocated (39,40). Both strategies may not be possible. Positioning is subject to coronary venous anatomy, lead delivery and stability, pacing thresholds, and phrenic nerve stimulation (36). Procedural limitations are inherent to device therapy.

Coronary artery disease presents many obstacles to resynchronization. Previous infarction impedes coronary venous access, particularly to the left marginal vein (41). High capture thresholds due to scarring further restrict lead placement. Aside from technical constraints, global scar burden and extent of viable myocardium directly correlate with remodeling after CRT (42,43). In addition, greater scar density around the pacing site portends an unfavorable response despite adequate lead thresholds (42,43). Poor recruitment of surrounding myocardium

Abbreviations and Acronyms

CI = confidence interval
CRT = cardiac resynchronization therapy
HF = heart failure
IVMD = interventricular mechanical delay
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
LVPEP = left ventricular pre-ejection period
NYHA = New York Heart Association
ROC = receiver-operator characteristic
ROI = region of interest
RT3DE = real-time 3-dimensional echocardiography
SPWMD = septal-to-posterior wall motion delay
SRI = strain rate imaging
TDI = tissue Doppler imaging
$T\varepsilon$ = time to peak strain
To = time to onset peak velocity
Ts = time to peak systolic velocity
TSI = tissue synchronization imaging

Table 1 Inclusion Criteria and Outcomes of CRT Trials

Study Acronym (Ref. #)	n	Design	Follow-Up (Months)	QRSd (ms)	Mean QRSd (ms)	LVEDD (mm)	Echocardiography	LVEF (%)	NYHA Functional Class	SR/AF	ICD	End Points		
PATH-CHF (1)	41	Cross-over	1	≥120	175 ± 32	No cutoff	No	No cutoff	III, IV	SR	No	6MWT + 44 m $p < 0.001$	MLHFQ −19.3 $p < 0.001$	Peak Vo_2 +1.8 $p < 0.001$
PATH-CHF II (2)	86	Cross-over	3	≥120	155 ± 20	No cutoff	No	≤30	II–IV	SR	Yes	6MWT + 47 m $p = 0.024$	MLHFQ −8.1 $p = 0.004$	Peak Vo_2 +2.5 $p < 0.001$
MUSTIC-SR (3)	48	Cross-over	3	>150	174 ± 20	>60	No	<35	III	SR	No	6MWT + 73 m $p < 0.001$	MLHFQ −13.6 $p < 0.001$	Peak Vo_2 +1.2 $p = 0.029$
MUSTIC-AF (4)	37	Cross-over	3	>200 paced	209 ± 18 paced	>60	No	<35	III	AF	No	6MWT + 32 m $p = 0.05$	MLHFQ −4.3 $p = 0.11$	Peak Vo_2 + 1.7 $p = 0.04$
MIRACLE (5)	453	Parallel	6	≥130	166 ± 20	≥55	No	≤35	III, IV	SR	No	6MWT + 29 m $p = 0.005$	MLHFQ −9.0 $p = 0.001$	NYHA $p < 0.001$
MIRACLE-ICD (6)	369	Parallel	6	≥130	164 ± 22	≥55	No	≤35	III, IV	SR	Yes	6MWT + 2 m $p = 0.36$	MLHFQ −6.5 $p = 0.02$	NYHA $p = 0.007$
MIRACLE-ICD II (7)	186	Parallel	6	≥130	165 ± 23	≥55	No	≤35	II	SR	Yes	6MWT + 5 m $p = 0.59$	MLHFQ −2.6 $p = 0.49$	Peak Vo_2 +0.3 $p = 0.87$
CONTAK-CD (8)	490	Parallel	6	≥120	158 ± 26	No cutoff	No	≤35	II–IV	SR	Yes	6MWT + 20 m $p = 0.043$	MLHFQ −2 $p = 0.39$	Peak Vo_2 +0.8 $p = 0.03$
COMPANION (9)	1,520	Parallel	16.2 median	≥120	160 median	≥60	No	≤35	III, IV	SR	Yes	Death, admission HR: 0.81 $p = 0.015$	Death HR: 0.76 $p = 0.06$	HF death, admission HR: 0.66 $p = 0.002$
CARE-HF (10)	813	Parallel	29.4 mean	≥150 ≥120 + echocardiography	160 median	30 height indexed	Yes (n = 92)	≤35	III, IV	SR	No	Death or MACE HR: 0.63 $p < 0.001$	Death HR: 0.64 $p = 0.002$	HF admission HR: 0.48 $p < 0.001$

AF = atrial fibrillation; CARE-HF = Cardiac Resynchronization in Heart Failure study; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure study; CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation; MLHFQ = Minnesota Living with Heart Failure Questionnaire; MUSTIC = Multisite Stimulation in Cardiomyopathies study; NYHA = New York Heart Association; PATH-CHF = Pacing Therapies for Congestive Heart Failure study; QRSd = QRS duration; SR = sinus rhythm; Vo_2 = oxygen consumption (ml/min/kg); 6MWT = 6-min walk test.

disconnects electrical and mechanical capture. Ischemic heart disease is consistently an independent predictor of lack of "response" (using surrogate outcomes) to CRT (19,29,44).

Severely remodeled ventricles are possibly "beyond repair," regardless of correctable dyssynchrony (45). Both severe LV dilation and mitral regurgitation independently predict adverse remodeling and clinical outcomes (19,46,47). This is not unexpected. Resynchronization coordinates existing contraction. Globally dilated, poorly contractile ventricles have limited capacity for improvement. Meta-analysis of clinical trial data may establish whether a diameter exists above which resynchronization is ineffective.

Device programming and optimization contribute to response. The acute hemodynamic benefit of optimizing atrioventricular delay is undeniable. Whether this translates into long-term improvements in remodeling, symptoms, or prognosis is unknown (48). Long-term outcome is also dictated by major adverse cardiovascular events, development of atrial fibrillation, changes in medical therapy, and duration of follow-up. Given the numerous reasons for nonresponse, we must consider how much incremental benefit echocardiographic selection may provide, and whether this will significantly change survival or hard clinical end points.

How Do We Measure Mechanical Dyssynchrony Using Echocardiography?

Mechanical dyssynchrony may be assessed using conventional M-mode and Doppler echocardiography. Newer modalities include tissue Doppler imaging (TDI), tissue synchronization imaging (TSI), triplane TDI, real-time 3-dimensional echocardiography (RT3DE), strain rate imaging (SRI), and speckle tracking strain.

What Are the Limitations of Echocardiographic Parameters?

Conventional measurements. Interventricular mechanical delay (IVMD) is the difference in left and right ventricular pre-ejection periods (LVPEP and RVPEP, respectively), measured from QRS onset to the beginning of aortic and pulmonary Doppler velocity curves, respectively (49). Both LVPEP and IVMD reflect a complex interaction between systolic function, pre-load, and afterload. Prolonged RVPEP in pulmonary hypertension or right ventricular dysfunction reduces IVMD and accuracy of assessment (50). Left lateral wall diastolic contraction describes delayed lateral wall contraction (using M-mode) after onset of diastolic filling (transmitral Doppler E-wave onset) (10,49,51,52). Coexistence of post-systolic contraction and diastolic relaxation signifies severe intraventricular dyssynchrony. Specificity is thus high, but sensitivity low.

Septal-to-posterior wall motion delay (SPWMD) measures time between maximal incursion of the septum and posterior wall on M-mode, with a delay ≥130 ms considered significant intraventricular dyssynchrony (23,30,51,53–56). Many drawbacks to SPWMD exist. It is 1-dimensional, comparing only 2 basal segments and neglecting the more frequently delayed lateral wall. Septal motion reflects interventricular in addition to intraventricular dyssynchrony (51). Feasibility is variably reported between 55% and 100% (23,30,51,53–56). Maximal septal or posterior wall motion is often diminished or absent in ischemic populations, causing inaccurate assessment (23,51,54,55). Parasternal acoustic windows may be inadequate (55). Perpendicular M-mode sections of the proximal LV are often not possible (23).

TDI. TEMPORAL VERSUS SPATIAL DYSSYNCHRONY. TDI evaluates longitudinal myocardial contraction in the basal and midsegments from apical 4-, 3-, and 2-chamber views. Either time to peak systolic velocity (Ts) or time to onset of systolic velocity (To) is measured relative to QRS onset. Intraventricular dyssynchrony is quantified either by the standard deviation of 12 segments (Ts-SD-12 or "dyssynchrony index") or the maximal temporal difference between 2 (Ts-2, To-2) or more LV segments (e.g., Ts-6, Ts-12). Larger values indicate more severe dyssynchrony.

Variance in timing alone cannot differentiate between spatial patterns of dyssynchrony. Reduced cardiac ejection occurs through displacement of blood volume from early to late activated regions. More contractile force is accommodated when delayed segments are clustered together. The net impact is less when delays are dispersed throughout the ventricle (57). Most of the proposed measures also ignore the apical segments completely.

ALIGNMENT. The limitations of TDI are similar to conventional Doppler. Excessive gain causes spectral broadening and velocity overestimation. Alignment of the insonating beam and direction of myocardial movement is crucial. Error is unavoidable given the limited number of acoustic windows through the human thorax. Deviation underestimates velocities and creates erroneous peaks through inclusion of nonlongitudinal motion. Alignment is particularly challenging in dilated, thinned, and spherically distorted ventricles.

LONGITUDINAL MOTION. Transducer orientation and insonation angle restricts TDI assessment to the longitudinal plane. However, ventricular contraction involves complex torsional deformation originating in oppositely wound myocardial fiber helices (57,58). In systole, the base rotates clockwise and apex counterclockwise (58). This wringing motion combines longitudinal, circumferential, and radial vectors. Of these, longitudinal indexes have several disadvantages: low amplitude, greater variance, and limited contribution to systolic function (57).

PULSED-WAVE ANALYSIS. Pulsed-wave and color-coded TDI are compared in Table 2. Pulsed-wave TDI is widely available and offers high temporal resolution. Sampling is restricted to a single position during each cardiac cycle, precluding post-hoc repositioning and analysis. Comparison

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Table 2 Differences Between Color-Coded and Pulsed-Wave TDI

Color-Coded TDI	Pulsed-Wave TDI
Limited availability	Wider availability
Myocardial velocities 10% to 20% lower compared with pulsed-wave TDI	Myocardial velocities 10% to 20% higher compared with color-coded TDI
Lower temporal resolution	Higher temporal resolution
Higher spatial resolution	Lower spatial resolution
Rapid acquisition	Slower acquisition
Offline analysis	Online analysis
Post-hoc sample volume repositioning possible	Post-hoc sample volume repositioning impossible
Simultaneous comparison of multiple segments	Simultaneous comparison of segments impossible

TDI = tissue Doppler imaging.

of multiple segments requires separate acquisitions in different cycles, and is limited by differences in heart rate, loading conditions, and respiration. Atrial fibrillation is notably problematic (24). By contrast, color-coded TDI stores time velocity data superimposed on 2-dimensional cine loops. This allows offline analysis of multiple segments within 1 plane during the same cardiac cycle.

TIMING VELOCITIES. Numerous issues confound timing of tissue Doppler velocities relative to the surface electrocardiogram. Error may result from imprecise identification of QRS onset, depending on morphology and electrical trace clarity. Measurement from a uniform point on the electrocardiogram is recommended if the QRS onset is unclear (59). The period during which to measure peak velocity is controversial. Analysis is typically confined to the ejection interval. The issue of post-systolic shortening is particularly problematic in ischemic populations. Some groups advocate extension into diastole (22,60,61). However, inclusion of post-systolic shortening yielded inferior results in comparative studies (62,63).

Inconsistent choice of peak velocity greatly impairs reproducibility. Suboptimal image quality, misalignment, translational vectors, and signal noise all create artefacts. Polyphasic or relatively flat velocity contours prevent uniform interpretation. Double peaks are common, especially in the free walls (64). Selection of the highest peak is advised (64–66). However, small variations in double peaks of similar amplitude often change selection and timing markedly (64). A recent study invited 9 expert faculty members of an international echocardiography congress to analyze velocity traces from 18 consecutive patients (45). Full agreement was achieved in just 3 cases, with an intraclass correlation coefficient of 0.42.

Measuring the time to onset of systolic velocity avoids errors in identifying peak velocity and is considered a surrogate for regional electromechanical coupling (46,50,67–70). However, the onset may be obscured by noise or fuse with the isovolumic contraction signal (71). The rationale for measuring time to onset as opposed to peak velocity depends on the perceived purpose of CRT. The former aims to synchronize ventricular depolarization, and the latter to synchronize mechanical contraction. Few studies have compared strategies, some favoring time to onset (67,72), others time to peak (71,73).

POSITIONING REGION OF INTEREST (ROI). Timing and velocities are neither homogeneous within segments nor abruptly demarcated between segments. Delayed contraction occurs in all segments and at all levels of the ventricle. Results are critically dependent on the location interrogated. Two post-processing steps introduce variability: placement and tracking of the ROI (74). Both lack standardization. Moving the ROI within segments significantly alters timing. Mean septal-lateral delay (Ts-2) was 28 ms higher when comparing low-basal and midbasal ROIs in 41 consecutive patients ($p < 0.01$) (45). Bland-Altman limits of agreement were correspondingly wide (±129 ms). Recent publications now advocate manually adjusting the ROI within the segment (up or down, left or right) to produce the most "representative" peak velocity (17,59). This is clearly highly operator dependent and contrasts starkly with the methods in earlier reports.

Once positioned, the segment of interest moves beneath a stationary ROI during the cardiac cycle. Manual ROI tracking, though time consuming, is required to maintain a midsegment location and avoid inclusion of the ventricular cavity. Stationary or manual ROI tracking may alter the location of the peak systolic velocity. ROI tracking changed the diagnosis of dyssynchrony in 3 of 18 patients (17%) when using 2- or 12-segment tissue Doppler models (74). No study examining prediction of response to CRT has specified whether or not ROI tracking was used.

REPRODUCIBILITY. Variability arises not only from intraobserver and interobserver differences, but also from sonographer technique, echocardiographic machines, and the physiological state of patients. Any index suitable for widespread screening should be obtainable and reproducible with different observers, sonographers, and equipment. Only 2 studies have reported test–retest reliability (65,71). Intraclass correlations were limited, ranging from $r = 0.26$ to $r = 0.56$ for 2- and 4-segment tissue Doppler models. Moreover, wide Bland-Altman confidence intervals (CIs) exceeded the diagnostic cutoffs for the respective criteria (65).

FEASIBILITY. Few studies have reported feasibility, given the aforementioned limitations (Table 3). Many enrolled nonconsecutive patients, or excluded patients with inadequate measurements from analysis (24,56,67,75). Whether the high-quality data acquisition translates to real-world patients with extensive comorbidity is questionable. Who arbitrates image quality and by what standards must be considered.

TSI. The TSI algorithm automatically detects peak systolic velocity. Color coding superimposed on real-time images displays regional delays, ranging from green (earliest) to red (latest). A quantitative tool automatically calculates the median Ts within a manually positioned sample volume,

enabling rapid comparison of segments (25,62). As with traditional TDI, moving the ROI within segments alters the measured delay. The TSI algorithm detects velocity peaks within a specified time interval. Systole must be manually defined according to aortic valve opening and closure. Incorrect timing introduces error through inclusion of peaks outside of the ejection phase.

Triplane TDI. Color-coded TDI only compares opposing walls within 1 plane. Interrogation of all segments requires 3 separate acquisitions in orthogonal planes, with unavoidable heart rate variability. A single 3-dimensional triplane dataset allows simultaneous comparison of all 12 segments during the same cardiac cycle. The technique reduces acquisition time, eliminates heart rate variability, and more accurately defines LV volumes (76,77). However, many inherent TDI failings remain: angle dependency, timing of peak velocities, ROI positioning, and assessment of only longitudinal motion.

RT3DE. Dyssynchrony may be characterized without TDI using a 3-dimensional model of the LV (78–80). Four consecutive cardiac cycles are combined to form a larger pyramidal volume (78,79). Acquisition requires end-expiratory breath hold and a stable heart rate to minimize translation artefacts between the 4 subvolumes. Application in patients with atrial fibrillation or frequent ectopy is limited. Regional time-volume curves allow measurement of time to minimum systolic volume. The standard deviation of 12 or 16 segments creates a systolic dyssynchrony index, expressed as percentage of the cardiac cycle (78–80). The parameter encompasses longitudinal, radial, and circumferential contraction. The problems are different, but no less significant, than those of TDI. Translational artefacts and suboptimal endocardial delineation often preclude analysis, confounding 23% of 100 patients with ischemic cardiomyopathy attending a high-volume center (80). Image quality was deemed optimal in only 34%. Lower frame rates and temporal resolution impede accurate timing. Time-volume curves are critically dependent on positioning of the center point, and are ambiguous for akinetic segments (80). Different software produces different values (78).

SRI. TDI myocardial velocities are inherently inaccurate through incorporation of translational cardiac motion, rotation, and tethering by adjacent segments. Strain (ε) measures localized myocardial deformation, thus differentiating between passive displacement and active systolic contraction. Dyssynchrony is characterized by dispersion of time to peak strain ($T\varepsilon$) between segments, analogous to TDI parameters (e.g., $T\varepsilon$-SD-12). Strain rate is traditionally derived from tissue Doppler velocities. High signal noise, artefacts, angle dependence, respiratory drift, and complex data processing all overshadow the theoretical merits (81). The resulting high intraobserver and interobserver variability limits reproducibility (63,82). Interpretation is difficult in ischemic populations as strain delays, particularly post-systolic shortening, may signify myocardial ischemia or viability rather than dyssynchrony (81).

Speckle tracking. Speckle tracking is a novel method of quantifying regional strain from routine B-mode gray-scale images (58,59,83). Tracking patterns of acoustic markers (speckles) quantify tissue deformation without the directionality constraints of Doppler techniques. Longitudinal and radial function are measured from apical and parasternal views, respectively. Several shortcomings exist. High quality, high frame rate, second harmonic images are required. Image degradation and through-plane motion both compromise speckle tracking (58). Temporal resolution is lower than TDI techniques. Conventionally, defining the ROI remains user dependent. The endocardial and epicardial borders are manually traced and fine-tuned to include all segments throughout the cardiac cycle (59,83). Further adjustment is undertaken to optimize the tracking stability score (59). An automated method for analysis has been developed but not yet applied to the assessment of dyssynchrony (84).

Agreement between modalities. Discordance between modalities raises further concerns. Studies have compared TDI against M-mode (55), conventional Doppler (72), RT3DE (79,80), and SRI (64). Agreement between modalities is limited (55,64,72,79,80). The reported prevalence varies significantly, despite recruitment of similar patients. Dyssynchrony is often present in asymptomatic normal subjects (64). In 2 studies (64,85), the average value of Ts-SD-12 in normal subjects exceeded the cutoff proposed for predicting response. Dyssynchrony appears to be defined largely by the method of assessment and threshold applied.

Predicting Response to Therapy

Numerous echocardiographic parameters have been proposed as predictors of response to CRT (Table 3). These largely derive from retrospective, exploratory analyses in small, single-center, nonrandomized studies. Whether or not consecutive patients were recruited and observers blinded is often unclear. Interpretation is confounded by varying definitions of dyssynchrony and response. The duration of CRT was frequently only 6 months or less, inadequate for assessing hard clinical end points. Intraobserver and interobserver variability are often quoted from previous studies or simply not presented. Cutoffs derived from 1 tissue Doppler parameter are inappropriately applied to another: 50 ms from 8- to 2-segment models (46,50); 65 ms from 4- to 2-segment models (21,55); 100 ms from 12- to 4-segment models (75,86). The majority of evidence derives from 3 academic programs in Hong Kong (17,62,63,87,88), Leiden (21,25,26,55,76–78,89,90), and Pittsburgh (59,83,91–93). Among these, it is uncertain whether patients from earlier studies were included in subsequent ones. Sensitivity and specificity are proportions for which CIs guide interpretation. Only 2 studies present such intervals (59,83). One hundred percent sensitivity and specificity are meaningless in small patient groups. In many studies, the lower CI would equate to tossing a coin. Results are often overinter-

Table 3 Design of Studies Investigating Parameters Predicting Response to CRT

First Author (Ref. #)	n	Follow-Up (Months)	Prospective	Consecutive Patients	Blinded Analysis	Dyssynchrony Parameter	Cutoff (ms)	Cutoff Derivation	Feasibility (%)	Variability	
										Intra-	Inter-
Conventional parameters											
Pitzalis (53)	20	1	Yes	Yes	Yes	SPWMD	130	ROC curve	100	0.96	0.91
Pitzalis (30)	51	14	Yes	Yes	Yes	SPWMD	130	Previous study	93	—	—
Marcus (54)	79	6	No	No	Yes	SPWMD	130	Previous study	55	High	High
Diaz-Infante (23)	67	6	Yes	Yes	Yes	SPWMD	130	Previous study	79	0.97	0.98
Sassone (51)	48	6	No	Yes	No	SPWMD	130	Previous study	67	—	—
						LLWDC	Present	Present/absent	96	—	—
Da Costa (95)	67	12	Yes	No	Yes	IVMD	50	Previous study	100	—	—
Achilli (46)	133	6	No	Yes	Yes	IVMD	44	ROC curve	100	—	—
Duncan (94)	39	6	No	No	Yes	t-IVT	—	—	100	—	—
Tissue Doppler imaging											
Bleeker (55)	98	6	No	Yes	Yes	Ts-2	65	Previous study	96	4%	10%
						SPWMD	130	Previous study	59	8%	14%
Bax (89)	25	Acute	No	Yes	Yes	Ts-2	60	Selected	100	—	—
Bleeker (26)	40	6	Yes	Yes	Yes	Ts-2	65	Previous study	100	—	—
Soliman (24)	60	12	No	Yes	Yes	Ts-2 pulsed	60	Previous study	93	Low	Low
Bax (21)	80	6	No	Yes	Yes	Ts-4	65	ROC curve	100	—	—
Heist (75)	39	Acute	No	Yes	No	dP/dt	600 mm Hg/s	Previous study	—	—	—
						Ts-4	100	Previous study			
Notabartolo (22)	49	3	No	Yes	No	Ts-6	110	EP study	100	—	—
Yuan (109)	18	3	Yes	Yes	Yes	Ts-6 annular	105	ROC curve	100	—	—
Yu (87)	30	3	No	No	No	Ts-SD-12	32.6	2 SD controls	100	<5%	<5%
Yu (63)	54	3	No	No	No	Ts-SD-12	31.4	ROC curve	100	3%	5%
Yu (88)	55	3	No	No	No	Ts-SD-12	31.4	ROC curve	100	—	—
						Ts-12	98.5	ROC curve			
Yu (17)	256	6	No	No	Yes	Ts-SD-12	33	ROC curve	100	5%	10%
						Ts-12	100	ROC curve			
						Ts-2	60	ROC curve			
De Boeck (45)	41	7	Yes	Yes	Yes	Ts-SD-12	32	Previous study	100	13%	—
						Ts-2	60	Previous study	100	11%	—
						IVMD	40	Previous study	100	14%	—
						Strain-2	150	Previous study	100	9%	—
Penicka (69)	49	6	Yes	Yes	Yes	To-3	60	ROC curve	100	7%	9%
						To LV-RV	56	ROC curve	100	6%	7%
						To sum	102	ROC curve	100	—	—
Jansen (67)	69	3	No	Yes	No	To-SD-6	20	ROC curve	100	3%	5%
						To-6	60	ROC curve	100		
Jansen (110)	53	3	No	Yes	Yes	Shuffle	Present	Present/absent	100	6%	11%
Cannesson (91)	23	8	Yes	Yes	No	Velocity vector	75	ROC curve	92	3%	4%

Continued on next page

Table 3 Continued

First Author (Ref. #)	n	Follow-Up (Months)	Prospective	Consecutive Patients	Blinded Analysis	Dyssynchrony Parameter	Cutoff (ms)	Cutoff Derivation	Feasibility (%)	Variability	
										Intra-	Inter-
Tissue synchronization imaging											
Tada (61)	22	27	No	No	No	TSI Ts Sep Lat	150	Selected	100	—	—
Gorcsan (92)	29	Acute	Yes	Yes	No	TSI Ts-2	65	ROC curve	100	4%	6%
Van de Veire (25)	60	6	No	Yes	Yes	TSI Ts-2	65	Previous study	100		
Yu (62)	56	3	No	No	No	TSI Ts-SD-12	34.4	ROC curve	100	4%	6%
						TSI Ts-12	105	ROC curve	100		
						TSI Ts-SD-6	34.5	ROC curve	100		
						TSI Ts-6	78	ROC curve	100		
3-dimensional											
Van de Veire (77)	49	Acute	No	Yes	No	3D Ts-SD-12	35.8	ROC curve	100	—	—
Van de Veire (76)	60	6	No	Yes	No	3D Ts-SD-12	33	ROC curve	100	—	—
Marsan (78)	56	Acute	No	Yes	Yes	3D SDI	5.6	ROC curve	93	Low	Low
Strain rate imaging											
Porciani (98)	59	6	Yes	No	No	oExcT	760	ROC curve	89	—	0.97
						Ts-SD-12	32	ROC curve	—	—	—
Mele (56)	37	6	Yes	Yes	Yes	Tε-SD-12	60	Median	97	0.99	0.97
						Tε-2 Sep-Post	194	Median	87	0.97	0.99
Dohi (93)	38	Acute	No	Yes	No	Tε-2 Sep-Post	130	Selected	97	2%	4%
Capasso (27)	28	12	Yes	Yes	No	Tε-2	—	—	—	—	—
Speckle tracking											
Knebel (101)	38	9	No	No	No	Tε-6	—	—	100	—	—
						Ts-6	105	ROC curve	100	—	—
Suffoletto (83)	50	8	Yes	Yes	No	Tε-2 Sep-Post	130	ROC curve	94	6%	8%
Gorcsan (59)	176	6	Yes	Yes	Yes	Tε-2 Sep-Post	130/60	ROC curve	93	—	—
Delgado (90)	161	6	No	Yes	No	Tε-2 Sep-Post	130	ROC curve	85	0.98	0.97

CRT = cardiac resynchronization therapy; dP/dt = delta pressure/delta time; EP = electrophysiological; IVMD = interventricular mechanical delay; Lat = lateral; LLWDC = left lateral wall diastolic contraction; LV = left ventricular; oExcT = total time of segmental contraction exceeding aortic valve closure Post = posterior; ROC = receiver-operator characteristic; RV = right ventricular; SDI = systolic dyssynchrony index; Sep = septal; SPWMD = septal-to-posterior wall motion delay; Tε = time to peak strain; t-IVT = total isovolumic time; To = time to onset peak velocity; Ts = time to peak systolic velocity; TSI = tissue synchronization imaging; 3D = 3-dimensional.

preted, without statistical confidence that observations are not simply the play of chance.

Predicting response using conventional parameters. Echocardiographic inclusion criteria in the CARE-HF (Cardiac Resynchronization in Heart Failure) study were in addition to, rather than replacing, intermediate QRS prolongation (120 to 150 ms) (10). Ninety-two (11%) patients were enrolled, requiring 2 of 3 echocardiographic indicators of dyssynchrony: LVPEP >140 ms, IVMD >40 ms, or left lateral wall diastolic contraction. By definition IVMD and LVPEP are highly interdependent, demonstrating collinearity in multivariate models (45).

A number of small, single-center studies observed no correlation between remodeling after CRT and IVMD, assessed using conventional or tissue Doppler (21,51,63). However, in other reports, IVMD predicted both clinical and volumetric response (45,94,95). Two multicenter studies have confirmed the importance of IVMD. The Italian SCART (Selection of CAndidates to cardiac Resynchronization Therapy) trial retrospectively analyzed 6-month outcomes in 133 consecutive patients, defining response by clinical composite score combined with improved LVEF ≥5% (46). Multivariate analysis identified longer IVMD as an independent predictor of positive response (odds ratio: 1.017 [95% CI: 1.005 to 1.029], p = 0.007). However, sensitivity and specificity were limited using the receiver-operator characteristic (ROC)-derived cutoff of 44 ms (66% and 55%, respectively). In the CARE-HF trial, prolonged IVMD was an independent predictor of response to CRT (hazard ratio: 0.99 [95% CI: 0.98 to 1.00], p = 0.0084) (96). A degree of caution is warranted, as both analyses were exploratory, and the interactions between IVMD and response were limited.

In 2 studies, SPWMD ≥130 ms predicted reverse remodeling in patients with predominantly nonischemic cardiomyopathy (n = 20 and n = 60) (30,53). Predictive accuracy (84% and 85%) and correlation between SPWMD and volumetric change were remarkably consistent. In the larger study, SPWMD ≥130 ms independently predicted long-term clinical improvement after CRT (median follow-up 14 months) (30). Five subsequent studies unequivocally refuted the clinical applicability and predictive value of SPWMD (23,51,54–56). Feasibility ranged from just 55% to 79% (Table 3). Baseline SPWMD consistently failed to differentiate between responders and nonresponders, or correlate with LV remodeling. Sensitivity ranged from 24% to 66%, and specificity from 38% to 66%.

Predicting response using TDI. The simplest tissue Doppler assessment, septal-to-lateral delay (Ts-2), predicted short-term remodeling and symptomatic response in studies from 3 centers (17,26,55,63,89). A retrospective analysis combined data from 256 patients attending these centers (17). Septal-to-lateral delay predicted LV remodeling at 6 months with a sensitivity of 70% and specificity of 76%. Less favorable results were obtained elsewhere in 60 and 41 patients (24,45). Sensitivity for identifying remodeling over similar time periods ranged from 33% to 62%, and specificity from 23% to 65%. Beyond the inherent limitations of TDI described previously, 2-segment models also neglect the majority of delayed segments. Interrogating more segments improved predictive accuracy in comparative studies (17,45,63,67).

The maximum time difference between peak systolic velocities in 4 basal segments (Ts-4) was examined in 85 patients (21). Dyssynchrony ≥65 ms yielded a sensitivity and specificity of 80% to predict clinical improvement and of 92% to predict reverse remodeling. Patients with dyssynchrony had improved prognosis compared with those without (6% vs. 50% 1-year mortality or HF hospitalization, p < 0.001). Contrary evidence emerged from the Italian multicenter SCART trial (46). Time to onset of systolic velocity was measured using pulsed-wave Doppler in 133 consecutive patients. Septal-to-lateral delay (To-2) failed to predict the composite clinical and remodeling end point in multivariate analysis. Subgroup analysis further discredited TDI techniques (68). Despite employing a more complex 6 basal segment model, neither clinical nor volumetric response differed in patients with dyssynchrony.

Yu et al. (17,62,63,87,88,97) have championed the 12-segment "dyssynchrony index" (Ts-SD-12). All but 1 report assessed remodeling at 3 months, defined as reduction in left ventricular end-systolic volume (LVESV) by 15% (17). The original study included 30 patients (87). The dyssynchrony index was the only independent predictor of reverse remodeling, with a pre-implant cutoff of 32.6 ms completely separating responders from nonresponders. Four subsequent reports included 54, 55, 56, and 58 patients, all with similar baseline characteristics (62,63,88,97). Whether separate patient cohorts were involved is unclear. For predicting remodeling, sensitivity ranged from 94% to 100%, and specificity from 78% to 100% (63,87,88,97). Accuracy was similar in a combined analysis of 256 patients attending the universities of Hong Kong, Leiden, and Pittsburgh (17). Whether comparable results are attainable beyond academic institutions is doubtful. Two other single-center studies have failed to reproduce such high predictive values (45,98). Ts-SD poorly predicted volumetric remodeling after 6 months in 41 and 59 patients. Sensitivity was reasonable (83% and 82%, respectively) but specificity poor (24% and 39%, respectively). As discussed later, the feasibility, reproducibility, and predictive accuracy of tissue Doppler parameters were shown to be inadequate in the multicenter PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial (99).

Predicting response using TSI. The Hong Kong and Leiden groups compared automatic TSI and manual TDI parameters in 56 and 60 patients, respectively (25,62). High correlations validated the TSI software (r = 0.97 and r = 0.95, respectively, both p < 0.001). Baseline TSI dyssynchrony was significantly greater in responders (25,62), and correlated with volumetric change after CRT (Table 4) (62,100,101). Predictive accuracy for remodeling was similar in 2-, 6-, and

12-segment parameters. Furthermore, the method of quantifying dispersion was only of minor importance. Measurement of standard deviation or range yielded similar overall accuracy and correlations in both the 6- and 12-segment models. No multicenter or randomized trial has employed TSI techniques.

Predicting response using triplane TDI. One group has assessed acute and longer-term prediction of response using triplane TDI (76,77). Close correlations were noted between conventional and triplane Ts measurements (r between 0.94 and 0.98, $p < 0.001$). In 60 consecutive patients, Ts-SD-12 predicted improvement in NYHA functional class at 6 months with 89% sensitivity and 82% specificity (76).

Predicting response using 3-dimensional echocardiography. Studies have demonstrated short-term improvement in dyssynchrony and predicted acute volumetric response using 3-dimensional echocardiography (78,79,102). None has assessed prediction of longer-term response.

Predicting response using SRI. The evidence supporting tissue Doppler-derived strain is no less contradictory than for tissue Doppler techniques. Three nonrandomized, single-center studies reported positive results using different strain parameters (56,93,98). Utilizing Tε in 38 and 37 patients, respectively, delay between anteroseptal and posterior walls predicted acute increase in stroke volume (93), while the standard deviation of 12 segments correlated with remodeling 6 months after CRT ($r = -0.73$, $p < 0.001$) (56). The third report proposed a novel parameter reflecting the total time of segmental contraction exceeding aortic valve closure (98). A cutoff of 760 ms predicted 6-month remodeling with 94% sensitivity and 83% specificity.

Three reports by Yu et al. (17,63,88) contest the utility of SRI. All tissue Doppler, but no strain rate measurements, predicted 3-month remodeling when comparing 18 parameters (63). The largest study included 256 patients attending 3 academic centers (17). Again, none of the longitudinal strain parameters predicted reverse remodeling after 6 months. The areas under the ROC curves barely deviated from the "no utility" value of 0.50 (range 0.49 to 0.53, all p = NS).

Predicting response using speckle tracking. Once more, the evidence is conflicting. Three studies from Leiden and Pittsburgh found that delay ≥130 ms in peak septal-to-posterior wall radial strain predicted remodeling after at least 6 months, defined by ≥15% improvement in LVEF or LVESV (59,83,90). Sensitivity ranged from 83% to 89%, and specificity from 73% to 83%. Speckle tracking and TDI methods were highly correlated ($r = 0.94$, $p < 0.001$) (83). However, neither demonstrated clear superiority (83,90). A German single-center study contradicted these positive results (103). Both radial and longitudinal speckle tracking strain failed to predict reverse remodeling 6 months after CRT in 38 patients.

Will Combining Parameters Improve Patient Selection?

No single parameter will completely dictate CRT response. Some have proposed combining methods or using scoring systems (59,69,75,104). In the Pittsburgh speckle tracking study, combining longitudinal and radial measures predicted ejection fraction response with 88% sensitivity and 80% specificity, significantly better than either technique alone (59). The St. Mary's protocol from London selected from 2 major and 6 minor dyssynchrony criteria, mixing conventional and tissue Doppler measures of intraventricular and interventricular dyssynchrony alongside QRS duration (104). No formal validation was published. Scores encompassing periprocedural variables are limited in selecting patients before implantation (75).

The PROSPECT Study: Predictors of Response to CRT

The multicenter PROSPECT trial was expected to inform the cardiology community of the best echocardiographic predictor of response to CRT (99). The trial proved to be more informative than expected. All 53 centers in the U.S., Europe, and Hong Kong obtained independent accreditation before enrollment of nearly 500 patients. A specific echocardiographic protocol was approved by the steering committee. The robust study design incorporated site training in acquisition methods and blinded analysis in 3 core international laboratories.

The study exposed critical limitations in the 12 echocardiographic measures of dyssynchrony and questioned the validity of previous single-center experience. Feasibility of tissue Doppler measurements was poor, with the percent of individual parameters deemed interpretable ranging from just 37% to 82%. Studies considered uninterpretable by the core laboratories were excluded from further analysis. Even among evaluable echocardiograms, the lack of reproducibility was striking. For 6- and 12-segment TDI models, the respective intraobserver variability was 16% and 11%, and interobserver variability was 32% and 34%. Differences in echocardiographic platforms and equipment were also apparent. TDI data obtained with the Siemens (Malvern, Pennsylvania) machines were excluded from analysis because of suboptimal data quality as determined by the core laboratories (99).

As well as lacking reproducibility, the parameters also lacked meaningful predictive value. Sensitivity for identifying improvement in clinical composite score ranged from 6% to 74%, and specificity from 35% to 91%. Prediction of reverse remodeling, defined as reduction in LVESV by 15%, was no better. For all parameters, the area under the ROC curve for positive clinical or volumetric response was ≤0.62. Several explanations for the findings have been postulated. These include differences in the study population compared with those of previous reports and unfamiliarity with parameters of dyssynchrony at the individual centers. Nonetheless, the extensive training ensured that quality was far above that expected in routine clinical practice. The results make it impossible to endorse any echocardiographic measure of dyssynchrony to select patients for CRT.

Table 4 Parameters of Systolic Dyssynchrony Predicting Response to CRT

First Author (Ref. #)	Responder Definition	% Nonresponders	Dyssynchrony Parameter	Responders vs. Nonresponders		Correlation*		Accuracy	
				Parameter (ms)	p Value	r	p Value	Sn	Sp
Conventional parameters									
Pitzalis (53)	15% LVESV	40	SPWMD	246 vs. 110	<0.001	0.70	<0.001	100	63
Pitzalis (30)	5% LVEF	53	SPWMD	—	—	0.69	<0.0001	92	78
Marcus (54)	15% LVESV	—	SPWMD	77 vs. 59	0.63	0.10	0.41	24	66
Diaz-Infante (23)	Death, transplant, 6MWT 10%	25	SPWMD	158 vs. 144	0.7	—	—	47	48
	15% LVESV	56	SPWMD	—	—	0.2	0.1	50	38
Sassone (51)	15% LVESV	35	SPWMD	96 vs. 108	0.555	—	—	—	—
			LLWDC	9 vs. −12	0.003		Independent predictor		
			IVMD	46 vs. 52	0.308	—	—	—	—
Da Costa (95)	HF death or admission, transplant	30	IVMD	64 vs. 57	0.09		Independent predictor		
Achilli (46)	5% LVEF, Clinical Score	32	IVMD	52 vs. 36	0.029			66	55
Duncan (94)	NYHA ≥1	26	t-IVT	16 vs. 9 (s/min)	<0.001	—	—	—	—
			IVMD	59 vs. 9	<0.001	—	—	—	—
Tissue Doppler imaging									
Bleeker (55)	NYHA ≥1	23	Ts-2	103 vs. 41	<0.05	—	—	90	82
			SPWMD	188 vs. 155	NS	—	—	66	50
Bax (89)	5% LVEF	32	Ts-2	86 vs. 39	<0.01	0.47	0.017	76	88
Bleeker (26)	NYHA ≥1 and 6MWT ≥25%	40	Ts-2	—	—		Independent predictor		
Soliman (24)	NYHA ≥1 and 6MWT ≥25%	17	Ts-2 pulsed	—	—	—	—	62	20
	15% LVESV	22	Ts-2 pulsed	81 vs. 78	NS	—	—	62	23
Bax (21)	NYHA ≥1 and 6MWT ≥25%	26	Ts-4	87 vs. 35	<0.01	—	—	80	80
	15% LVESV	—	Ts-4	—	—	0.70	<0.001	92	92
Heist (75)	ΔdP/dt ≥25%	54	Ts-4	—	—	0.60	<0.0001	100	38
			dP/dt	—	—	0.47	0.002	89	76
Notabartolo (22)	15% LVESV	41	Ts-6	289 vs. 188	<0.01	—	—	97	55
	NYHA ≥1, 6MWT 50 m, QOL 15	24	Ts-6	264 vs. 198	—	—	—	78	33
Yuan (109)	5% LVEF	39	Ts-6 annular	111 vs. 86	0.005	0.79	0.033	86	73
Yu (87)	15% LVESV	43	Ts-SD-12	45.0 vs. 24.8	<0.001	0.76	<0.001	100	100
Yu (63)	15% LVESV	43	Ts-SD-12	—	—	0.74	<0.001	96	78
Yu (88)	15% LVESV	47	Ts-SD-12	—	—	0.76	<0.001	96	78
			Ts-12	—	—	0.64	<0.001	90	76
Yu (17)	15% LVESV	45	Ts-SD-12	46 vs. 29	<0.001	—	—	93	73
			Ts-12	137 vs. 91	<0.001	—	—	92	68
			Ts-2	90 vs. 42	<0.001	—	—	70	76
De Boeck (45)	15% LVESV	41	Ts-SD-12	47 vs. 42	NS	0.27	0.086	83	24
			Ts-2	29 vs. 32	NS	0.12	0.453	33	65
			IVMD	67 vs. 41	<0.01	0.46	0.003	91	47
			Strain-2	330 vs. 182	<0.01	0.45	0.003	96	47

Continued on next page

Table 4 Continued

First Author (Ref. #)	Responder Definition	% Nonresponders	Dyssynchrony Parameter	Responders vs. Nonresponders		Correlation*		Accuracy	
				Parameter (ms)	p Value	r	p Value	Sn	Sp
Penicka (69)	25% LVEF	45	To-3	84 vs. 38	<0.0001	—	—	85†	77†
			To LV-RV	84 vs. 43	<0.0001	—	—	85†	64†
			To Sum	167 vs. 81	<0.0001	0.73	<0.0001	96	77
Jansen (67)	15% LVESV	45	To-SD-6	37 vs. 20	<0.0001	0.59	<0.0001	97	74
			To-6	—	—	0.59	<0.0001	95	73
Jansen (110)	10% LVESV	30	Shuffle	—	—	—	—	87	69
Cannesson (91)	15% LVEF	43	Velocity vector	131 vs. 52	<0.05	—	—	85	80
Tissue synchronization imaging									
Tada (61)	15% LVESV	45	TSI Ts Sep Lat	303 vs. 176	<0.05	—	—	100	90
Gorcsan (92)	15% stroke volume	48	TSI Ts-2	161 vs. 18	<0.001	—	—	87	100
Van de Veire (25)	NYHA ≥1 and 6MWT ≥25%	43	TSI Ts-2	79 vs. 28	<0.001	—	—	80	92
	15% LVESV	47	TSI Ts-2	78 vs. 37	<0.001	—	—	81	89
Yu (62)	15% LVESV	46	TSI Ts-SD-12	47.3 vs. 29.2	<0.001	0.61	<0.001	87	81
			TSI Ts-12	133.9 vs. 83.7	<0.001	0.60	<0.001	83	85
			TSI Ts-SD-6	42.9 vs. 26.6	<0.001	0.52	<0.001	70	92
			TSI Ts-6	105.2 vs. 65.5	<0.001	0.53	<0.001	73	77
3-dimensional									
Van de Veire (77)	15% LVESV	53	3D TSI Ts-SD-12	44 vs. 23	<0.0001	0.59	<0.001	91	85
Van de Veire (76)	NYHA ≥1	37	Ts-SD-12 3D	42 vs. 22	<0.001	—	—	89	82
	15% LVESV	42	Ts-SD-12 3D	44 vs. 20	<0.001	0.52	—	90	83
Marsan (78)	15% LVESV	37	3D SDI	9.7 vs. 3.4	<0.0001	0.60	<0.0001	88	86
Strain rate imaging									
Porciani (98)	15% LVESV	53	oExcT	1,087 vs. 663	<0.001	0.48	0.0001	94	83
			Ts-SD-12	50 vs. 37	<0.01	0.32	0.01	82	39
Mele (56)	15% LVESV or 20% LVEF	35	Tε-SD-12	—	—	0.73	<0.001	—	—
Dohi (93)	15% stroke volume	45	Tε-2 Sep-Post	249 vs. 137	<0.005	0.93	<0.0001	95	88
Capasso (27)	NYHA ≥1 and 6MWT ≥25%	21	Tε-2	87 vs. 91	NS	—	—	—	—
Speckle tracking									
Knebel (101)	15% LVESV	53	Tε-6	168 vs. 179	NS	—	—	—	—
			Ts-6	121 vs. 107	—	—	—	64	80
Suffoletto (83)	15% LVEF	24	Tε-2 Sep-Post	223 vs. 120	<0.05	—	—	89	83
Gorcsan (59)	15% LVEF	34	Tε-2 Sep-Post	—	—	—	—	84	73
Delgado (90)	15% LVESV	45	Tε-2 Sep-Post	251 vs. 94	<0.001	0.41	<0.001	83	80

*Correlation between dyssynchrony parameter and responder definition; †accuracy parameters calculated from data presented.

LVESV = left ventricular end-systolic volume; QOL = quality of life; Sn = sensitivity; Sp = specificity; other abbreviations as in Table 1.

Table 5 CRT in Patients With Narrow QRSd

Study/First Author (Ref. #)	n	n With Narrow QRSd	Randomized	Control Group QRSd	Prospective	Blinded	Follow-Up (Months)	Echocardiographic Parameter	Main End Points
RethinQ (66)	172	172 <130 ms	Yes	CRT off Narrow	Yes	Yes	6	Ts-4 SPWMD	Peak Vo_2 ≥1.0 46% vs. 41%, p = 0.63
Yu (104)	102	51 <120 ms	No	Wide ≥120 ms	Yes	No	3	Ts-SD-12 ≥32.6 ms	No significant difference: 6MWT, NYHA, LVEF, LVESV
Bleeker (105)	66	33 <120 ms	No	Wide ≥120 ms	Yes	Yes	6	Ts-4 ≥65 ms	No significant difference: 6MWT, NYHA, LVEF, LVESV
Achilli (106)	52	14 ≤120 ms	No	Wide >120 ms	Yes	Yes	18 mean	IVMD LLWDC	No significant difference: NYHA, LVEF, LVESD, MR
Gasparini (107)	376	45 ≤120 ms	No	Wide >120 ms	Yes	No	28 mean	None	No significant difference: mortality, 6MWT, NYHA, LVESV
Gasparini (111)	158	30 <150 ms	No	Wide ≥150 ms	Yes	No	11 mean	None	No significant difference: 6MWT, QOL, LVEF, LVESV

LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; other abbreviations as in Tables 1 and 3.

Echocardiographic Dyssynchrony in Patients With Narrow QRS Complexes

What is a narrow QRS? The 120 ms QRS threshold adopted by international guidelines is based on the enrollment criteria of landmark clinical trials. However, the true meaning of "narrow" QRS duration is controversial. The median QRS duration in both the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF studies was 160 ms, while the mean QRS duration ranged from 155 to 175 ms in the remaining trials (Table 1). This has prompted many to question the benefit of CRT in patients with an "intermediate" QRS duration between 120 and 150 ms (105). In the CARE-HF and COMPANION trials, only those patients with QRS ≥160 ms and ≥169 ms, respectively, experienced a significant risk reduction (9,10). Such retrospective, subgroup-derived dichotomies are misleading. While efficacy and dyssynchrony may correlate, this does not justify extrapolating arbitrary, non–pre-specified cutoffs to patient care. QRS duration is a continuous variable whose threshold must reflect the entry criteria of landmark clinical trials. In these trials the number and outcomes of patients with an intermediate QRS duration is unknown.

Echocardiographic selection in narrow QRS patients. Three nonrandomized, single-center studies have compared CRT in patients with broad and narrow QRS durations (120 ms cutoff), the latter selected using tissue Doppler or conventional parameters (Table 5) (106–109). All 3 studies were small, including between 14 and 51 patients. All 3 reported no significant difference in clinical and remodeling end points, including NYHA functional class and LVEF. However, the largest narrow QRS study to date yielded similar results without echocardiographic selection. In 331 and 45 patients with a wide and narrow QRS, respectively, increases in NYHA functional class, LVESV, and 6-min walk distance were similar over a mean 28-month follow-up (110). The echocardiographic studies were critically flawed. None included a narrow QRS control group without echocardiographic dyssynchrony or without CRT activated. No hard clinical end point was evaluated. Most importantly, failure to detect a difference does not imply equivalence.

The only randomized trial in patients with a narrow QRS confirms these misgivings. After device implantation, the RethinQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) trial randomly assigned 172 patients with echocardiographic dyssynchrony to CRT or no CRT (66). Most patients (96%) were selected using tissue Doppler criterion (Ts-4 ≥65 ms). After 6 months, neither the primary end point of peak oxygen consumption nor other indicators such as reverse remodeling or 6-min walk distance improved. In summary, no robust evidence supports echocardiographic selection in patients with a narrow QRS. An appropriate trial would require a reproducible measurement of dyssynchrony tested prospectively with hard clinical end points.

Cautions Regarding the QRS Duration

The QRS duration is not perfect. It represents the vectorial sum of electrical forces generated by myocardial masses over time. Simplicity is both a strength and weakness. The electrocardiogram is an inexpensive, rapid, and reproducible tool obtainable in every patient by anyone with basic technical training. More importantly, in randomized controlled trials, the QRS duration identified patients likely to gain significant morbidity and mortality benefits from CRT. Nevertheless, QRS duration is only a surrogate for timing of myocardial contraction. Correlations with interventricular and intraventricular mechanical dyssynchrony are limited (111). The electrocardiogram is unable to characterize the presence, direction, and severity of delay in each ventricular segment. Regional abnormalities with small electrical vectors are undefined. Echocardiography in principal offers solutions to these problems. Newer modalities such as speckle tracking will hopefully prove more feasible and reproducible in randomized controlled trials and clinical practice. Only then will the benefits of CRT be extended to patients with a narrow QRS duration.

Conclusions

International guidelines are clear and unanimous in defining who should receive CRT (11–15). The Class I, Level of Evidence: A recommendations contain only 1 measure of dyssynchrony: QRS prolongation. Landmark clinical trials have demonstrated unequivocal morbidity and mortality benefits in over 4,000 patients enrolled on the basis of their electrocardiogram. Echocardiographic dyssynchrony has been the subject of numerous publications and is proposed by some as a superior means of selecting patients for CRT. Echocardiographic parameters have largely been studied in small, nonrandomized studies with surrogate end points. Major methodological limitations include lack of basic validation and demonstration of reproducibility. The largest trial of such measures, the PROSPECT trial, demonstrated striking variability, poor reproducibility, and limited predictive power when applied in clinical practice. Echocardiographic measures should not be used to deny patients potentially life-saving therapy or expose them to unnecessary risks. Patient selection must use the parameter prospectively validated in landmark clinical trials: the QRS duration.

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